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COVID-19
PHARMACOLOGIC TREATMENT

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9 April 2020

COVID-19 Pharmacologic Treatment

There is no directed therapy for COVID-19. The standard is best supportive care – as is the case for many viral illnesses. Therefore, any current use of pharmacotherapy is 'off-label' and at the discretion of the treating doctor in consultation with the patient on a case-by-case basis. Ideally, such prescription would be undertaken as part of a formal clinical trial – of which there are numerous currently recruiting (or about to recruit) around the world.

There is, however, seminal interest surrounding several existing agents that might be 're-purposed' to treat COVID-19, in addition to the plasma from recovered individuals. The current (scant) evidence of leading contenders will be briefly reviewed. All of the reviewed therapies are the subject of imminent or ongoing clinical trials.

Convalescent plasma infusion/exchange

As a last resort in the SARS/MERS and Ebola pandemics, immunotherapy using virus-specific antibodies in convalescent plasma was used to improve survival rates of patients with serious infections. The best effect was in SARS when administered early with a pooled odds of mortality of 0.25[1]. There are numerous case reports of this occurring in COVID-19 with some success[2].

When disease is fulminant, patients may develop sepsis, acute respiratory distress syndrome (ARDS), and/or multiple organ failure. Treatment of the systemic response to COVID-19 involving the complex interaction of cytokine storm, inflammation, endothelial dysfunction, and pathologic coagulation is likely to be helpful[3]. Therapeutic plasma exchange offers benefit, therefore, on multiple levels by removing cytokines, stabilising endothelial membranes, and resetting the hypercoagulable state.

Nucleoside analogues

Nucleoside analogues target the RNA polymerase responsible for replication of viral RNA causing termination of viral genome replication by accumulating mutations and blocking entry of incoming natural nucleotides[4].

Favipiravir is a guanine analogue approved for treatment of influenza, which can inhibit replication of Ebola, yellow fever, norovirus, and enterovirus[5]. It shows effective anti-viral activities in vitro[5]. Favipiravir can be combined with other anti-viral agents such as interferon-α.

Ribavirin is also a guanine analogue, used in the treatment of hepatitis C and respiratory syncytial virus. It has also been used in SARS and MERS, but without great success[5,6,7]. Side effects are also a problem, such as anaemia. Ribavirin has been postulated to be used in lower-dose combination for COVID-19 with pegylated interferon to stimulate innate anti-viral responses[4]. Molecular work suggests the COVID-19 RNA-dependent RNA polymerase model is targeted by ribavirin[1]. There is in-vitro success with this drug in COVID-19[8].

Remdesivir is an adenine analogue (similar to tenofovir used as a reverse transcriptase inhibitor in HIV) designed for Ebola, which has shown activity against MERS and SARS in-vitro and in mice[9]. Therapeutic efficacy was confirmed in Ebola in a phase III clinical trial[10]. Remdesivir has been prescribed to some COVID-19 patients[11], and demonstrated antiviral activity in vitro[5]. There are phase III clinical trials underway to test clinical efficacy of remdesivir in COVID-19. Results will be declared this month, but it is suggested remdesivir improves lung function, reduces lung viral loads, and ameliorates severe lung pathology[1]. These results were superior to prophylactic and treatment protease inhibitors with interferon-β.

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Anti-malarial/Anti-inflammatory drugs

Chloroquine works in malaria by concentrating in lysosomes raising pH to cause lysosomal dysfunction, heme build-up and cell lysis[12]. It also has anti-viral activities by inhibiting endosomal acidification (required for virus-host cell fusion) and interfering with glycosylation of the cellular receptor of SARS[4,13]. Both drugs have immunomodulatory effects that can suppress the immune response[1]. Anti-viral activity of chloroquine has been demonstrated against Ebola, SARS, MERS and Hendra[4]. The efficacy of chloroquine in-vitro has been established against COVID-19[5]. Chloroquine/Hydroxychloroquine has been trialled in >100 patients with COVID-19 pneumonia and been reported to be superior to control treatment in inhibiting the exacerbation of pneumonia, improving chest imaging findings, promoting virus-negative conversion, and shortening the length of illness[14]. These reports suggest 'severe' side effects were not noted.

Hydroxychloroquine is an analogue of chloroquine that has fever concerns about drug interactions[1]. In pharmacokinetic models, hydroxychloroquine was found to be more potent than chloroquine in COVID-19 in-vitro[1]. In a small (n=20) open label trial of hydroxychloroquine 600mg daily with the discretionary addition of azithromycin, there was a significant reduction in viral load on serial nasopharyngeal swabs at day 6 and lower average carrying duration compared to controls[15]. The addition of azithromycin improved virus elimination. Worryingly, when there was an attempt to replicate these results by another French group in 11 hospitalised patients, the results were starkly inferior and suggested no greater benefit[16]. In a small series (n=30) of treatment, naïve patients given either hydroxychloroquine 400mg a day or standard care there was no difference in negative COVID-19 conversion rate on pharyngeal swab at day 7 or clinical/radiologic improvement[17].

Protease Inhibitors

Protease inhibitors bind and inhibit viral proteases responsible for proteolytic cleavage of large polyproteins, encoded by viral genome, which are required for viral gene expression and replication[4]. Both lopinavir and ritonavir are currently used in HIV treatment and are reported to have anti-viral activities against SARS and MERS (in combination with ribavirin)[18].

However, a recent randomised trial comparing lopinavir/ritonavir with standard care showed no additional benefit[19]. There were approximately 100 patients in each arm and the protease inhibitor combination was not associated with improvement in time to clinical improvement, reduced mortality, or reduced viral RNA levels.

In a modified intention-to-treat analysis, the lopinavir/ritonavir combination led to a median time to clinical improvement gain of one day. Gastrointestinal side effects were more common in the treatment arm, and therapy was ceased early in 14% of patients.

AP2-associated protein kinase-1 inhibitors (AAK1 inhibitors)

Baricitinib is a high affinity AAK1-binding drug that binds with another regulator of endocytosis (movement of virus into cell), the cyclin G-associated kinase. It has less toxicity than other drugs of this class and may be an agent to consider against COVID-19[20].

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Angiotensin Converting Enzyme & Fusion proteins

Angiotensin converting enzyme 2 is the main receptor for SARS-CoV-2 binding to cells to initiate entry of the virus into the soon to be infected cell. ACE2 is a transmembrane glycoprotein that normally cleaves angiotensin II and thus regulates the Renin-Angiotensin System. It is expressed in lungs, heart, kidneys, intestines, and testes[21,22,24]. A proposed ACE2-fused protein potentially prevents infection by interfering with this key virus-cell interaction by binding to the receptor binding domain of the COVID-19 S protein that binds to ACE2 to gain cell entry[24]. The fusion protein (ACE2-Ig) is constructed from the extracellular domain of human ACE2 receptors, linked to the Fc domain of human IgG1. Variants of molecules that block this key interaction are being considered[25].

Furthermore, the ACE2 protein can be cleaved at the cell surface to release the extracellular region which retains enzymatic activity - soluble ACE2 (sACE2). Soluble ACE2 can bind to the S-protein of SARS-CoV and inhibit entry/infection of cells. The infection mechanism of SARS-CoV and SARS CoV-2 (COVID-19) is the same so it is presumed sACE2 can also inhibit infection of COVID-19[21]. The Chinese have developed a method to aerosolise sACE, and clinical trials of this formulation are underway.

There are no data to support the notion that ACE inhibitor or angiotensin II type 1 receptor blocker administration facilitates coronavirus entry by increasing ACE2 expression in either animals or humans[22]. There are reports of angiotensin receptor blockers and angiotensin converting enzyme inhibitors being associated with lower rates of severe disease and a trend towards a lower level of IL-6 in peripheral blood (systemic inflammation)[26]. This might be via higher levels of ACE2, which are protective against ARDS[23].

Corticosteroids

Current WHO recommendations advise against routine use of prednisolone in the management of severe acute respiratory infections from COVID-19. Past experience in SARS, MERS, and other similar outbreaks do not support the regular use of steroids and there is a possibility of harm[1]. Case reports still exist, however, of complex patients managed with steroids[27], sometimes in low dose. Clinical trials utilising different dosing regimens are underway.

'Novel' anti-viral agents

Arbidol is a broad-spectrum anti-viral drug that inhibits virus-mediated fusion with a target membrane and a resulting block on virus entry[28]. It has traditionally been used in influenza, but invitro activity against SARS as well as COVID-19 has been demonstrated[29].

Anti-viral Interferons

Type I IFNs are antiviral cytokines that induce a large range of proteins that can impair viral replication in targeted cells. Previous studies have reported that IFN-β was superior against SARS-CoV compared to IFN-α. Synergistic effects of leukocytic IFN-α with ribavirin and IFN-β with ribavirin against SARS-CoV were demonstrated in-vitro[28].

In the SARS-CoV outbreak, the most widely used treatment regimen in China was ribavirin and interferon, based on studies showing efficacy of this combination in reducing viral replication and disease severity in animal models[30]. One prospective study underway is of interferon-α paired with either ribavirin, lopinavir/ritonavir, or all three drugs in a randomised trial in COVID-19.

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Antibiotics

Teicoplanin is an antibiotic commonly used in treatment of severe gram-positive infections with a spectrum of activity similar to vancomycin. Its mechanism of action is to inhibit cell wall synthesis[31]. It has been found to be active in-vitro against SARS-CoV, but also Ebola, Influenza, flavivirus, and MERS[32]. In coronaviruses (such as MERS and SARS), teicoplanin inhibits the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes, thereby preventing the release of viral RNA and continuation of the viral life cycle. A recent study has shown this attenuating activity is present in COVID-19[33].

Anti-parasitic drugs

Ivermectin is a commonly used anti-parasitic drug recently shown in Australia to have in-vitro activity against COVID-19, among other viruses such as dengue, influenza, and HIV[34]. This is principally through inhibition of the critical interaction of RNA viruses with the importin α/β1 heterodimer associated with nuclear importation of viral proteins. A single dose in-vitro was able to significantly reduce viral replication within 24-48 hours. Ivermectin has established safety in humans.

Checkpoint inhibitors

The cytokine storm produced in some COVID-19 patients with severe disease can cause significant organs dysfunction and cause death. Thus, treating this inflammatory response may be critical. Interleukin-6 plays an important role in cytokine release syndrome[35].

Tocilizumab is a recombinant humanised monoclonal antibody against human interleukin 6 (IL-6) receptor of immunoglobulin IgG1 subtype. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signal transduction. It has been approved for the treatment of rheumatoid arthritis. There are small case series of patients with relatively severe disease in China treated with tocilizumab showing improvement[36].

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